As the Royal Society for Biology (RSB) was forming 10 years ago, antimicrobial resistance (AMR) was being heralded as the next threat with a magnitude on a par with global warming. Just a few years later, in 2016, Jim O’Neill’s report was published laying out recommendations for tackling drug-resistant infections globally. Where are we now, and what are the challenges ahead? As a slow burner, how will the impact of AMR compare against the recent rapid devastation of the COVID-19 pandemic, and how can we channel some of the good things that come from it (like the awareness and technique of effective hand hygiene) to help us combat AMR speedily and definitively?

Antimicrobials and resistance against them
Since the antibiotic penicillin was made available to customers through pharmacists in 1945, it has been vital for saving lives. However, even in the speech delivered by Alexander Fleming when he received his Nobel Prize, there was a warning that resistance against antimicrobials could emerge and prevent effective treatment of infections.

Many different antibiotics have been discovered since, and these are crucial to our health, underpinning everyday treatments including chemotherapy for cancer, joint replacement surgery and transplant surgery.

The antibiotics in our arsenal were primarily discovered in the first twenty years succeeding penicillin, and they represent diverse chemistries (e.g. β-lactams like penicillin, aminoglycosides, peptides, macrolides, quinolones) with cellular targets that include the cell wall/membrane plus intracellular machineries, including those involved in the maintenance of the genetic code, protein synthesis and metabolism [1]. An innovation gap of ~40 years began in the 1960s, during which the main classes of antibiotics that were discovered from natural sources were chemically tailored to alter their target efficacy. Since 2000 there have been a few more antibiotic classes discovered e.g. oxazolidinones, lipo-peptides, mutilins, fi oxomicin and diarylquinolones [2]. However, in 2017 a patient died from an infection caused by a Klebsiella pneumonia that was resistant to every available antibiotic in the USA, highlighting the urgent need for antibiotic scaffold diversification [3].

Antimicrobial resistance (AMR) occurs naturally. For example, in the soil many microorganisms exist, some of which produce molecules (e.g. secondary metabolites) with antimicrobial activity. In this environment, the ability to resist antimicrobials is selected for, although there is more than one explanation for this. Whilst it could be to avoid death from the antimicrobial, it is likely that the natural level of the molecule is below the killing dose. At such sub-lethal levels, the molecule may induce a stress response in neighbouring bacteria that increases the chance of mutations occurring during replication of genetic material. If a mutation occurs that provides a slightly faster growth rate, the resultant fitness advantage will provide an advantage [4]. AMR mechanisms are as diverse as the antimicrobials, and include (i) preventing the entry of the antibiotic, (ii) pumping the antibiotic out, (iii) inactivating the antibiotic, or (iv) changing the antibiotic’s target so it can no longer work e.g. by modifying the target structure so it is not compatible, producing an alternative machinery so that inhibition of the target does not affect the growth of the microbe, or overproducing the target so that
the effects of inhibition are diluted [1]. Since AMR-encoding genes can be transferred by genetic exchange
between microorganisms, they can be introduced into different populations. The major problems arise when
AMR-encoding genes reach pathogens, especially in the context of the clinic where vulnerable individuals are
plentiful. Since the 1960s the levels of detected AMR have been rising, such that at the turn of the century the
World Health Organisation (WHO) released a report describing the major global threat of AMR. It is striking
how rapidly the first reported case of resistance follows on from the year an antibiotic is introduced into a
clinic [5]. It is also noteworthy how fast AMR can spread across the globe. For example, the New Delhi
metallo-β-lactamase 1 (NDM-1), an enzyme that makes bacteria resistant to a broad range of β-lactam antibio-
tics including the carbapenem family, spread to more than 80 countries in just a few years after its initial iden-
tification in the mid-2000s [6].

Why is AMR a crisis?
We have come to rely on the use of antibiotics, and as a consequence we use a lot of them. In 2016, the UK
used >60 Tonnes of antibiotics in their hospitals, but this pales into the background against the global annual
use across all sectors, since USA had an antibiotic footprint of 8361 Tonnes when their use in human con-
sumption, the community, hospitals and, most significantly animal agriculture was considered [7]. If the anti-
biotics are rendered useless by AMR, there will therefore be a considerable impact on our lives, given the broad
effect AMR has on the microbiosphere locally and globally [8–11].

In 2016, the O’Neill report set out the evidence that AMR is responsible for >700 000 deaths per year across
the globe and predicted that by 2050 this figure will reach 10 million per year [12] which will have a significant
impact on the economy and existing health services. The predicted morbidity will include deaths from condi-
tions that can currently be corrected by routine surgery (e.g. hip replacement) or chemotherapy (e.g. cancer),
because the risk of subsequent AMR infections becomes life-threatening. The report laid out 10 recommenda-
tions to avoid this potential calamity (Figure 1).

Developments to tackle AMR
In the four years since the O’Neill report [12], there has been some progress that includes the publication of a
new AMR strategy in the UK [13] and a surveillance programme [14]. To build on the momentum that has
achieved a reduction in the antibiotic usage in humans (7.3%) & food-producing animals (40%) between 2014–
17 (UK), the strategy outlined the goals to (i) reduce UK antibiotic use in food-producing animals by 25% between 2016 and 2020, and to define new objectives by 2021 for 2025, plus (ii) be able to report on the percentage of prescriptions supported by a diagnostic test or decision support tool by 2024. It will be interesting to monitor this if the promised EU legislation relating to this comes into force in 2022, and whether the UK commits to it post-Brexit.

The release of potential new antibiotics onto the market gets delayed by the length of time it takes to ensure they are safe and effective. Also, profits for the company selling the antibiotic will be delayed by the new antibiotic being kept on the shelf as a ‘last resort’ to provide a treatment option to patients infected by a bacterium resistant to all the other available antibiotics [2,15–18]. To provide new incentives to promote investment for new drugs and improvement of existing ones, the UK strategy included a new payment model for the NHS that de-couples the price paid for antimicrobials from the volumes sold. At the recent Westminster Health Forum: ‘Antimicrobial resistance—progress on the UK strategy and coordinating a global response’ (February 20th, 2020), the proposal was mooted to think more in terms of the future value of preventing AMR i.e. using a life insurance model to align the value of the antibiotic with the cost of the procedures its use would prevent.

The 2019 UK AMR strategy pledged that the outcome of the measures it outlined would be firstly to halve the number of healthcare-associated Gram-negative blood stream infections per year. However, the UK AMR strategy did not indicate whether a robust surveillance monitoring procedure existed or had to be introduced to identify when infection is prevented. A second intended outcome of the UK AMR strategy was a 10% reduction in the number of specific drug-resistant infections in humans by 2025, but the document did not clarify which drugs that the resistance would be against.

A review in 2019 [19] of the progress made in the fight against AMR since the report in 2016 [12] summarised a positive global impact of measures aimed at reducing AMR including an advocacy tool, raised international profile of AMR and the stimulation of new initiatives e.g. funding of early-stage research in the field. However, it did not find a lot of progress made towards transforming research and development incentives for antibiotics, vaccines and diagnostics. Moreover, despite significant advances in reducing antibiotic use in agriculture, there was still a long way to go in Low and Middle Income Countries (LMICs). The underlying reasons for the limited changes being realised in LMIC were outlined as (i) the challenge to restrict over-the-counter sales of antibiotics in the face of poor living conditions and access to healthcare, and (ii) unhygienic conditions in the community and in healthcare facilities, contributing to high rates of infection and limiting the impact of messages about awareness and infection prevention and control. Taking these together, the recommendations of the 2019 review were to focus on the crucial interventions of providing universal high quality health coverage and investing in water, sanitation and housing. The review noted that such an agenda would only be effective if it informs the operations of governments and funding agencies such as the International Monetary Fund (IMF) and the World Bank. The overriding conclusion was that the current emerging innovations in the global governance of AMR need to lead to action rather than more words. For example, has the greater investment in awareness raising changed behaviour, and whilst investments have been made in improving surveillance of antibiotic use and resistance, particularly for humans, more effort is required to create surveillance systems that provide sufficiently accurate data to influence policy and action, and that this applies to both antibiotics and resistant genes circulating in the environment [19,20].

In the UK, changes are being motivated by a new NHS hygiene improvement policy [21] with the vision to support a ‘common understanding’ among healthcare staff and aim to reduce variation of practice and standardise care processes (Figure 1). However, from the global perspective, there might be a particular issue amongst displaced people and in refugee camps where wounds caused by conflict are common and hygiene is particularly difficult to maintain.

**New threats with an AMR component**

**Bacterial biofilm communities**

The antibiotics available today have been discovered through their ability to eradicate free-living, individual bacteria. The amount of resistance to an antibiotic is also determined by measuring the concentration of an antibiotic that inhibits the growth of bacteria in liquid suspension (Minimum Inhibitory Concentration, MIC) in standardised conditions. However, more bacteria exist in biofilm communities, than as free-living bacteria. Biofilms are complex, co-ordinated communities that bacteria form on surfaces. The surfaces may be abiotic e.g. pipes, or biotic e.g. a tooth or wound. Biofilms consist of the bacteria embedded inside an extracellular...
matrix comprising of proteins, polysaccharides and nucleic acid. Antibiotics do not easily penetrate through this matrix, the microenvironments they encounter may render them less effective, and the bacteria within biofilms are physiologically altered due to initiating stress responses that might include a form of dormancy known as persister cells. All of this combines to make bacteria in biofilms difficult to eradicate [22]. Moreover, biofilms often contain more than one species, and these may interact to alter their susceptibility to antibiotics [23]. Biofilms can also serve as a reservoir for AMR determinants or a site where AMR determinants are exchanged between bacteria, however, there is more to be understood about how and when this occurs [24,25].

New ways to manage biofilms are being discovered based on the knowledge that they are recalcitrant to antibiotic therapy, and using the ever-growing understanding of the architecture, environmental niches, developmental stages and molecular mechanisms functioning in biofilms. For example, new surfaces to which bacteria do not attach are being developed to reduce biofilm formation (e.g. polymer-coated indwelling devices, manipulation of surface topology [26,27]), and the effectiveness of novel antimicrobial delivery mechanisms is being assessed in the context of biofilms [28]. In parallel, improved diagnostic kits that can handle the challenge of detecting AMR in biofilms are required to enhance prescribing practices. The PHE Antimicrobial Stewardship Toolkit for English Hospitals [29] highlights the need for quality assurance in diagnostics, but more research is required to optimise accurate detection of AMR in biofilms and correlate this with clinical outcome [30,31].

**Pandemics**

The COVID-19 pandemic can be traced back to a first case on 17th November 2019. Since then and going to press (April 14th 2020), there have been more than 1,952,385 cases, with a devastatingly high death toll of 122,790 people [32]. Not only is the world suffering from the consequences of this new infection on our health, but also on our economy and broader society.

How does this compare to the consequences of AMR? Approximately 2000 people worldwide die every day as a result of infections caused by resistant bacteria. So, in the same time period (17th November 2019–14th April 2020), 312,000 people will have died from the effects of AMR. Whilst the speed of COVID-19 infection and the consequent overwhelming of the global health services plus the lower capacity of our societal activities have had an impact on us to which it will take a long time to recover, the predicted impact of AMR by 2050 will also be significant, with many millions of people dying each year. The types of infection impacted by AMR may mean that many medical interventions that are currently routine by virtue of the availability of antibiotics, become impossible. The World bank has estimated that by 2030 the global GDP may fall by 1.1 (3.8%), forcing an additional 24 million people into extreme poverty. The cost on global healthcare may range from 300 to more than 1 trillion dollars [33].

Have secondary AMR infections combined to create the unprecedented impact of the COVID-19 pandemic? Recent summaries about this intersection are being pulled together regularly by the React group [34]. Currently, it is unclear if antibiotics administered to sufferers of COVID-19 have failed to work and contributed to the death of some of them. The verified numbers available are small, and the patients so weak when they contracted secondary infections, that death may have been inevitable. In the published study looking at 191 hospitalised adults in Wuhan, China and diagnosed with COVID-19, it was found that half of the patients that died (27/54) also had a secondary infection that had been treated with antibiotics. These secondary infections happened at a late stage of the disease (median time after the illness first began was 17 days). The severe symptoms (including sepsis and acute heart/kidney injuries) could have been caused by the SARS-CoV-2 virus since sepsis occurred in all the patients who did not survive whilst injury to the heart occurred in 59% and injury to the kidney to 50% of them. In time, when the data from more studies are available, it will be possible to draw firmer conclusions, and this is likely to be informed by research undertaken in countries that exhibit a higher underlying burden of AMR as the pandemic spreads more widely, despite our best efforts to contain it [35–38].

A more hidden impact of the pandemic on AMR may be a negative effect on the antibiotic supply chain given the key roles that China and India play in the production of antibacterials, and monitoring this closely as lockdowns are lifted will play a vital role in minimising this. The COVID-19 pandemic will hopefully come to an end, and an effective vaccine developed in the medium term to protect us going forward. Can there be additional good measures from this experience that can help us in the fight against AMR?

The pandemic has sparked a mass of publicity about the way to undertake effective hand hygiene and how it can be the single most effective measure to stop the spread of infection. Can we build on this momentum with steps to maintain this good practice and embed it into our everyday behaviour so that we do not have to resort
to the more drastic social distancing interventions? Learning from the experience with the pandemic, other vital strategies towards which resources should be deployed would include fast affordable diagnostics, new vaccines and new antimicrobials that include non-conventional approaches would provide long term solutions. In the meantime, the power of better public and professional awareness to galvanise preventative action against infections has been well demonstrated by the pandemic (Figure 2).

The way forward

There is certainly a will to win the battle against AMR with 82 864 people (14/4/2020) pledging to become an antibiotic guardian [39]. People are actively engaging in the search for new antibiotics using Citizen Science (e.g. the initiative Antibiotics Unearthed [40] and researchers in academia and industry are sharing their resources (e.g. through the Shared Platform for Antibiotic Research and Knowledge, SPARK [41], The Antibiotic Resistance Project ARP team of Pew Charitable Trusts [42], and React group [43].

There are cutting edge technological platforms being applied to the investigation of antimicrobial activity, and their improved resolution is enabling the studies that have focussed on genomics and transcriptomics to move towards metabolomics (e.g. Raman Spectroscopy [44,45] and Mass Spectrometry [11,46]). It is becoming evident that care must be taken when investigating combination treatment approaches to augment antimicrobial efficiency since in some instances they work synergistically [47], but in others one biocide can induce tolerance to another antibiotic [48]. However, there is promising evidence that repurposing of drugs (e.g. ones previously FDA approved) could be a speedy way forward to boost our antimicrobial weaponry since safety

Figure 2. A selection of the ways that effective hand hygiene has been communicated to the public during the COVID-19 pandemic.

The government initiated regular announcements in a range of forms including TV infomercials and posters on bus stops. The media has broadcast the hand hygiene and social distancing protocols, and promoted individual endeavours in all the different streams (TV, radio, newspapers). Celebrities and influencers have got on board by posting a range of material including songs, videos, poems, art by artists including Gloria Gaynor, Dame Judi Dench, Maria Carey. Information has been posted online and in social media by individuals and groups such as the public, businesses and the NHS e.g. Twitter #handwashing. This takes the form of practical guidance, and hard hitting poignant messages that may be spoken, danced, sung or written. Some take novel approaches at the protocol e.g. using black ink instead of soap to demonstrate how to cover all the hand during the 6 recommended steps of effective hand hygiene [49]. Blogs are collating opinions and previous research in the field is regaining attention e.g. http://glo-yo.co.uk and outreach activities revisited [50].
regulations will already have been undertaken [49,50]. Moreover, following the identification of new types of antibiotics from a pool of >100 million molecules [51], there may be a role for artificial intelligence-led discovery in this approach. Less conventional antimicrobial approaches may also bear fruit in the long run, e.g. using bacteriophage that are viruses that kill bacteria as a treatment [52], reinvestigating ancient medicines [53,54], manipulating the microbiome to defend against pathogen colonisation [55,56], targeting virulence rather than essential cellular processes so that bacteria are weakened in their pathogenicity but not killed so that there is no selection pressure for AMR [57]. This may be best suited as a combination treatment with a bactericidal agent [28,58].

Perhaps prevention is better than cure, and first and foremost, a focus on novel vaccine development may be required. Since (at least before the pandemic), the global population is rising, and alongside it the thousand times more numerous microbiome, it is conceivable that the AMR exchange between us, the environment and our fellow inhabitants of the planet is rising faster than hygiene can control [8].

In conclusion, AMR has been recognised as a global and significant issue that will affect both our health and the economy. Reviews have been undertaken, and recommendations suggested. Progress is being made towards the targets that pave the way to overcoming the threat of AMR. There is broad input into this progress, and yet we still have a long way to go, and we have to integrate new challenges into the roadmap (e.g. the LMIC environment and biofilms) as well as capitalising on unexpected developments (e.g. increased public awareness of effective hand hygiene during the pandemic).

**Summary**

- AMR is a clear and present danger: It kills a significant proportion of the population and has an economic impact.

- Recommendations made in the O’Neill Report (2016) remain relevant [12], and although some progress has been made and strategies have been put in place to move further forward, we cannot become complaisant as not all the recommendations have been addressed, and none of them have been fully delivered.

- New challenges within AMR lie ahead since biofilms are difficult to eradicate with the currently available antibiotics, and they represent the majority of bacteria and can serve as a reservoir of AMR. Overcoming the AMR hurdles is thus likely to require unconventional, novel strategies including vaccination.

- There is an opportunity to maintain the momentum of the improved hygiene measures imposed during the COVID-19 pandemic to stimulate long term behavioural change that will contribute to reducing AMR.

- Global equality is key to overcoming AMR: LMIC face significant and specific challenges that require solutions and there is a one health dimension to AMR since it exists in the human and animal population as well as the environment.

**Competing Interests**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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K.R.H. wrote the manuscript.

Abbreviations
AMR, antimicrobial resistance; IMF, International Monetary Fund; LMIC, low and Middle Income Country; MIC, minimum Inhibitory Concentration; NDM-1, New Delhi metallo-β-lactamase 1; PHE, Public Health England; RSB, Royal Society of Biology; UK, United Kingdom; WHO, World Health Organisation.

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